J Anesth (1995) 9:374–375

Journal of
Anesthesia

A successful case in cancer pain management with high-dose intravenous morphine

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Key words: Cancer pain management, High-dose morphine, PCA

Introduction

Patients with cancer pain sometimes experience so-called crescendo pain which escalates in intensity within short periods of time. Physicians who are not very familiar with morphine treatment may hesitate in such cases to increase the dose, probably because of a firm opposition to "morphinism."

We present a case in which a high dose of intravenous morphine (300 mg/h) was necessary to control severe cancer pain. In this case, rapid increase and high-dose morphine resulted in adequate pain relief without undesirable side effects such as addiction, respiratory depression, or a higher tolerance for morphine.

Case report

A 36-year-old woman with recurrent rectal cancer was referred to our clinic for uncontrollable severe pain in her left femoral region. Previous palliative treatment such as radiotherapy and oral morphine (240 mg/day) could not achieve sufficient pain relief. Evaluation of the pain revealed a vertebral metastasis. A trial of morphine infusion (200 mg/day) resulted only in nausea and drowsiness, but epidural morphine (150–200 mg/day) in combination with lidocaine (90–120 mg/day) by the patient controlled analgesia (PCA) system achieved good control without the major side effects related to narcotics use. Two months later, tumor invasion to the epidural space made epidural injection impossible. We therefore changed from epidural morphine to 500 mg/day i.v. morphine (bolus and background infusion by the PCA system) in combination with intravenous dexamethasone (0.5 mg/day), oral imipramine (50 mg/day) and carbamazepine (200 mg/day). However, the pain increased abruptly, which might be attributed to involvement of the spinal cord or roots by the tumor, so that the dose of morphine had to be increased rapidly to 300 mg/h, with which adequate pain relief was finally achieved. Within a week, her requests for analgesics declined dramatically, and the dose of morphine was tapered off gradually. She reported that numbness had replaced her pain, and paralysis was also clinically observed in her legs. Three weeks after the peak running dose, pain management was carried out satisfactorily with continuous infusion of morphine 200–300 mg/day. During the course of tapering off the dosage, she showed no withdrawal symptoms such as perspiration, tachypnea, or loss of pain control.

Discussion

Despite the wide acceptance of WHO methods for cancer pain relief [1,2], the pharmacological properties of morphine do not seem to be sufficiently understood. According to a report, only 13.8% of physicians who responded to a questionnaire would have clearly informed their patients of the fact that they were receiving morphine, and the rate of complete pain relief remained at less than 40% [1]. It is also worth noting that the amount of morphine consumed per capita in Japan is still less than one-fifth of that consumed in the United States and Great Britain [2]. These findings imply that many doctors tend to correlate morphine use with narcotic abuse. They relate increasing morphine doses to a higher tolerance and a consequent dependence on the drug.

In these circumstances, Hayashi et al. reported two cases of high-dose morphine administered orally. They

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Received for publication on January 22, 1994; accepted on June 9, 1995

positively titrated the dose to the patients' pain intensities and finally adequate pain relief was achieved by the administration of more than 5000 mg/day of morphine [3]. Since they did not measure the serum or cerebrospinal fluid concentration of morphine, the optimal doses could be smaller than 5000 mg/day. Oral administration did not always confirm the minimum dosage necessary for the patients, especially in cases of digestive cancer due to malabsorption. Hashimoto et al., on the other hand, reported two cases of continuous intravenous infusion of high-dose morphine [4]. They suggested that the third step of the WHO analgesic ladder had been mostly inadequate for their terminal cancer patients and recommended continuous infusion of morphine, though the doses they used were still only 12 mg/h and 20 mg/h, which were far smaller than ours.

In our case, a high dose of morphine was necessary to obtain adequate pain relief. Two reasons for our employing high-dose morphine are suggested: (1) severe neuropathic pain caused by tumor involvement, and (2) the possibility of a lower serum concentration of morphine than would be expected considering the high dose.

In general, the compression of the spinal cord or roots can cause severe pain, and this pain tends to increase rapidly. Anticonvulsants, antidepressants, and corticosteroids are usually recommended as adjuvant drugs of analgesics [5]. Despite administering all of the above drugs to the patient, we could not achieve adequate pain relief in our case without increasing the morphine dose. Systemic administration of local anesthetics has been reported to provide an analgesic effect on neuropathic pain [6], so it may be possibile to reduce the dose with intravenous lidocaine.

When an opioid is administered intravenously, the serum concentration of the drug is predictable to a certain extent. It has been reported, however, that a patient with chronic cancer pain requiring high-dose intravenous hydromorphone exhibited a far lower serum concentration than anticipated [7]. The etiology of these confusing results can still only be speculative; an accumulation of morphine in the abdominal or pleural effusion, or interstitial edema could account for the low serum concentration [8]. Though we did not measure the morphine serum concentration in our case, there was no clinical evidence of abdominal or pleural effusion, except mild edema observed in the lower limbs.

Also a morphine metabolite, morphine-3-glucuronide (M3G) has been shown to be an antagonist of the opiate receptor for both morphine and morphine-6-glucuronide (M6G) [9,10]. Therefore, the overall analgesic effect may be influenced not only by the serum or CSF concentration of morphine but by the ratio of M3G to M6G [11]. The reason for the high morphine dose in our case may be speculative, however, since no concentrations of analgesics were measured.

Tolerance could also be a factor in the high-dose morphine. Arnér et al. reported that the development of tolerance was considered a significant problem in spinal morphine treatment for cancer pain [12]. In our case, however, tolerance did not seem important because a small supplemental rescue dose proved to be effective and the dose was tapered without any problems.

In summary, we successfully managed a patient with severe cancer pain with an initially high morphine dose and a subsequent reduction of this dose without any undesirable side effects.

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